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INTERACTION PATTERN OF FULLERENE FAMILY WITH DIFFERENT FORMS OF DNA

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Abstract— Fullerenes have attracted considerable attention due to their unique chemical structure and potential applications. In this study fullerenes (C20 to C180) were interacted with different forms of DNA i.e. A, B and Z-forms. And no such change in the binding score was observed with the change in the sequence of DNA. In fact, binding score increases with the increase in the molecular weight of the fullerene while interacting with A & B-form of DNA but Z-form of DNA shows no regular pattern of binding. Number of interacting base pairs increases as the molecular size of fullerene increases. And the groove binding depends on the form of DNA, fullerene and fullerene family binds in major groove of A-DNA while binds in both major and minor grooves in B and Z-form of DNA. This study reveals that binding pattern of fullerene family with DNA, which can disrupt its structure and may leads to several biological errors.

Index Terms— , A, B, Z- DNA. Fullerene, Fullerene family

1 INTRODUCTION

THe Integrity and stability of DNA is essential to life, any damage to DNA not repaired causes mutation leading to disease. DNA can be damaged by many sorts of mutagens, include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays[1]. Various types of DNA damages include single and double strand break as in case of ROS such as the 8-oxoguanine and formamidopyrimidine [2], interacalation of chemicals between strand causing distortion as by 1, 4-naphthoquinone derivatives & quinacrine [3, 4], attachment of alkyl group to the DNA base as by sulphur and nitrogen mustard, methylation or ethylation of bases [5,6]. Whereas some chemicals are initially chemically inert they are metabolically converted into highly reactive compounds which can react with DNA forming adducts, i.e., chemical entities attached to DNA. Damage to DNA appears to be the major cause of most cancers and genetic birth defects and may also contribute to aging and heart diseases as well. Therefore, the analysis of chemical/physical agents to which humans are frequently/inevitably exposed, becomes mandatory for their capability to induce DNA damage.

In recent past, a new group of compounds known as nanomaterials have found tremendous applications with the advent of nanotechnology. A number of in vitro as well as in vivo studies have proven that these nanomaterials are also capable of inducing DNA damages [7-9] .Fullerenes, nanosized allotropes of carbon, due to their unique properties are used in number of fields such as chemical, material science including biomedical applications [10] .The first fullerene molecule discovered was buckminsterfullerene (C60), also termed as bucky ball, and consists of 20 hexagons and 12 pentagons. Fullerenes also occur naturally in the form of C60, C70, C82, C84 molecules whereas C24, C30, C40 etc can be produced by various industrial processes. Because of small size and easy entry into the human body, they get readily adsorbed to macromolecules affecting the regulatory mechanism of enzymes and proteins. Fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, tube and many other shapes. Special fullerenes are also called buckyballs and the cylindrical one are called carbon nanotubes or buckytubes. Past toxicological studies have been conducted to analyze the interactions of DNA with carbon nanomaterials, including carbon nanotube (CNT) [11, 12] spherical fullerene [13] and carbon nanoparticle (CNP) [14]. Studies have found that ss-DNA forms helical wraps around SWNT and ss-DNA molecules can be inserted into carbon nanotubes [15]. Also the strong association of C60 molecules with ion channels, enzyme and antibodies where the binding depends on the particle size and native protein structures has been noticed [16]. Simulation studies conducted by [13] revealed that C60 strongly binds to nucleotides in aqueous solution at the hydrophobic ends or at the minor groove of the nucleotide. This C60-ssDNA binding can significantly deform the nucleotides.

Some studies revealed CNP -DNA binding leading to DNA aggregation in vivo and in vitro [16]. The binding mechanism of water-soluble C60 derivative-ss-DNA was found to be similar to native C60–DNA, while forming more stable C60–DNA complex [13]. Molecular dynamics study reveals the distortion of DNA/RNA by the fullerene [17]. It has been already reported that C60 can binds to DNA via hydrophobic interactions *in silico* [18]. Some *in vitro* studies are also done to investigate the toxicity mechanism of C60 in biological system show that C60 molecules may interfere with the biological functions performed by DNA, resulting in disruptions to DNA replication, transcription and repair processes [19]. More studies are needed to reveal the interactions of various species of fullerenes with DNA, and how this interaction may affect various biological functions. Therefore, the present study was designed to investigate the possible interactions of different forms of fullerenes from C20-C180 with different forms of DNA (A, B & Z-DNA) with various base sequences in order to investigate the comparative effect of molecular size of fullerene and their reactivity for various forms & sequences of DNA.

2 MATERIALS AND METHOD

2.1 Procurement of fullerene family

Nanotube Modeller is a program for generating XYZ co-ordinates of nano geometries (nanocone, nanotube, fullerenes, viruses etc.). Fullerenes of various molecular sizes were obtained through fullerene library of Nanotube Modeller. Generated geometries of C20, C24, C30, C40, C48, C50, C60, C70, C76, C80, C84, C90, C96, and C100 & C180 were viewed using the integrated viewer.

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2.2 Generation and Procurement of various forms and sequences of DNA

We generated A and B-forms of DNA with ten different sequences. The Z-DNA was generated with single sequence as it is formed by stretches of alternating purines and pyrimidines, e.g. GCGCGC. All

the forms of Double strand (ds) DNA were prepared using Discovery Studio visualizer. Chimera was used for energy minimization, removal of steric collision with the steepest descent 1000, steepest descent size 0.02 Å, conjugated gradient steps 1000 and the conjugate gradient step size 0.02 Å for the conjugate gradient minimization [20,21].

Different sequences of nucleotides of A and B-form of DNA were generated are shown in TABLE 1

S.No.	Sequence	A-DNA and B-DNA
1.	Seq 1	ATATGCGCATAT
2.	Seq 2	ATGCATGCATGC
3.	Seq 3	ATATATGCGCGC
4.	Seq 4	ATATATATGCGC
5.	Seq 5	ATATGCATATGC
6.	Seq 6	ATATATGCATAT
7.	Seq 7	GCGCATATGCGC
8.	Seq 8	GCGCATGCGC AT
9.	Seq 9	GCGCGCATGCGC
10.	Seq 10	GCGCGCGCATAT

TABLE 1- Different sequences of A &B-form of DNA

2.3 Docking and Binding modes study

Patchdock is Geometry based molecular docking algorithm [22]. It was aimed at finding docking transformations that yield good molecular shape complementarities. Such transformations, when applied, induce both wide interface areas and a small amount of streric clashes was applied to identify the binding modes of fullerenes with different strand of nucleic acid. This method employed three-dimensional transformations driven by local feature matching and spatial pattern detection technique, such as geometry hashing and pose clustering, to yield good molecular shape complementary with high efficiency. The clustering root mean square deviation (RMSD) was 4Å. Binding modes of fullerenes were analyzed using Pymol and Discovery studio.

3 Results

3.1 Effect of molecular size of fullerene on DNA binding

Docking of A, B & Z forms of DNA with 10 different random sequences of 12 base pair length was performed with fullerenes of various sizes (C20 to C180), in order to determine the effect of fullerene size on DNA binding. Different forms of DNA interacted slightly differently with fullerene.

All the sequences of A form of DNA show a common trend of increase in docking score with increasing size of fullerene from C20 (1876, seq 9) up to fullerene C90(6520, seq 9). Thereafter, the increase in size of fullerene resulted in decrease in docking score.

S.No.	Receptor	Ligand	seq1	seq 2	seq 3	seq 4	seq 5	seq 6	seq 7	seq 8	seq 9	seq 10
1	A-DNA	c20	1942	1978	2030	2172	2034	2020	1934	1928	1876	1914
2	A-DNA	c24	2408	2396	2520	2642	2488	2520	2412	2642	2316	2430
3	A-DNA	c30	3130	3114	3254	3318	3198	3254	3152	3070	3036	3114
4	A-DNA	c40	3772	3840	3878	3920	3872	3908	3832	3806	3742	3760
5	A-DNA	c48	4432	4466	4478	4498	4446	4538	4450	4424	4370	4366
6	A-DNA	c50	4544	4536	4544	4542	4542	4602	4470	4426	4374	4446
7	A-DNA	c60	4790	5028	4860	4886	5076	4838	5042	5040	5068	4938
8	A-DNA	c70	5132	5428	5224	5178	5254	5118	5270	5380	5406	5404
9	A-DNA	c76	5386	5562	5332	5418	5504	5378	5398	5602	5630	5516
10	A-DNA	c80	5596	5954	5734	5802	5778	5696	5648	5944	5980	5908
11	A-DNA	c84	5626	5992	5696	5706	5758	5664	5710	5994	5938	5934
12	A-DNA	c90	6086	6352	6182	6246	6152	6098	6274	6438	6520	6284
13	A-DNA	c96	5998	6244	6038	6016	6248	5978	6132	6436	6440	6124
14	A-DNA	c100	5722	5908	6304	6352	6254	6096	6516	6680	6490	6528
15	A-DNA	c180	4760	4940	6528	4288	5078	5156	4036	4674	4338	5278

TABLE 2: Docking score of A-DNA with fullerenes increases with increasing size of fullerene from C20 (1876, seq 9) up to fullerene C90 (6520, seq 9).

All the sequences of B-form of DNA showed increasing trend of docking score, except C60 & C100 with the increase in size of fullerene from C20 (2012, seq 1) to C180 (3882, seq 8). Whereas C60 (2626, seq 9) & C100 (3400, seq 4) showed a lower docking score for all the different sequences.

S.No.	Receptor	ligand	seq1	seq2	seq3	seq4	seq5	seq6	seq7	seq8	seq9	seq10
1	B-DNA	c20	2012	2062	2042	2076	2064	2042	2070	2062	2064	2030
2	B-DNA	c24	2124	2122	2128	2128	2122	2132	2124	2116	2104	2132
3	B-DNA	c30	2162	2188	2184	2196	2192	2184	2198	2188	2204	2174
4	B-DNA	c40	2528	2458	2530	2530	2528	2530	2416	2444	2418	2432
5	B-DNA	c48	2764	2822	2750	2830	2820	2830	2702	2688	2698	2700
6	B-DNA	c50	2778	3036	2852	2822	2858	2816	2800	2772	2770	2816
7	B-DNA	c60	2676	2686	2646	2646	2652	2656	2648	2680	2626	2672
8	B-DNA	c70	2974	2898	2910	2960	2984	2948	2982	2974	2918	2936
9	B-DNA	c76	3196	3098	3146	3176	3192	3174	3192	3132	3080	3110
10	B-DNA	c80	3268	3162	3254	3264	3310	3254	3264	3212	3212	3250
11	B-DNA	c84	3426	3410	3428	3410	3436	3418	3426	3410	3382	3406
12	B-DNA	c90	3472	3388	3474	3468	3492	3450	3506	3434	3412	3474
13	B-DNA	c96	3676	3562	3646	3608	3690	3588	3686	3600	3576	3588
14	B-DNA	c100	3460	3546	3418	3400	3592	3512	3490	3556	3414	3426
15	B-DNA	c180	3902	3888	3966	3964	3990	3994	3984	3882	3886	3934

TABLE 3: Docking of B-dNA with fullerenes shows increasing trend of docking score, except C60 & C100 with the increase in size of fullerene from C20 (2012, seq 1) to C180(3882, seq 8).

Apart from these two forms of DNA, Z-form showed totally different trend of docking score; the score increased from C20 to C48, then no regular pattern was determined, the docking score fluctuated with further increasing the size of fullerene from C50 to C180

S. No.	receptor	ligand	score
1.	zdna	c20	2970
2.	zdna	c24	3250
3.	zdna	c30	3580
4.	zdna	c40	3760
5.	zdna	c48	3874
6.	zdna	c50	3830
7.	zdna	c60	3568
8.	zdna	c70	3508
9.	zdna	c76	3608
10.	zdna	c80	3518
11.	zdna	c84	3668
12.	zdna	c90	3552
13.	zdna	c96	3626
14.	zdna	c100	2878
15.	zdna	c180	3412

TABLE 4: Docking score of Z-DNA with fullerenes shows no regular pattern.

3.2 Effect of base sequence on fullerene binding

To determine the effect of variation in base sequence of DNA, the docking score of different fullerene molecule with various DNA sequences was compared. As a periodic trend the number of interacting bases increased with increasing sizes of fullerene, independent of the sequence of DNA. In case of A-form of DNA C20,24,30& 40 are mostly interacting with two base pairs only, C48,50,60,70,76,80,90 are interacting with three base pairs, whereas further increase in size of fullerene from C96 to C100, four bases were involved and C180 appear to involved up to five base pair in most sequences.

In B-DNA, C20, 24, 30, 40 interacted with one base pair only whereas on further increase in size of fullerene from C48 to C60 two base pair were involved, and from C70 to C100 three base pair were involved and for C180 four base pair were involved in most of the sequences. For Z-form of DNA, two base pair were involved from C20 to C80, but on further increase in the size of fullerene from C84 to C100, three base pair were involved and C180 involved four base pair as shown in figure-1 with the help of graph.

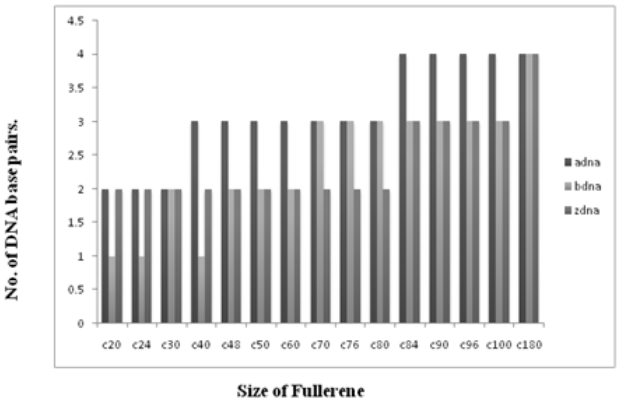

FIGURE 1: Effect of increase in molecular size of fullerene on the number of interacting DNA base pairs.

It was observed that the variation of sequence of DNA in all forms did not cause any effect on the binding efficiency of any type of fullerene. C20 fullerene was docked with all the sequence and scored in the range of 1942-1914 2013-2030 and 2970 for A, B and Z-form of DNA. C180 fullerene docked with different sequence of various forms of DNA with score in the range of 4760-5278, 3902-3934 & 3412. Docking score range of C24 to C100 are already discussed in Table-1, 2 &3.

3.3 Effect of Form of DNA on interaction with Fullerene

To determine the effect of forms of DNA (A, B & Z-DNA), all three forms of DNA were docked with various fullerenes of fullerene family (C20, 30, 40, 48, C60…..180) of different molecular weight. Each form interacts with fullerene in a different way. In A-form of DNA, increase in the binding score was observed from C20 to C90 followed by decrease in binding score with increase in molecular weight of fullerene. Whereas, B form of DNA showed continuously increase in binding score of with the increase in of fullerene size, barring C60 & C100. Strangely, Z-DNA displayed indefinite pattern in fullerene size dependent variation in docking score. This is explained with the help of graph by comparing all the three DNA's binding score.

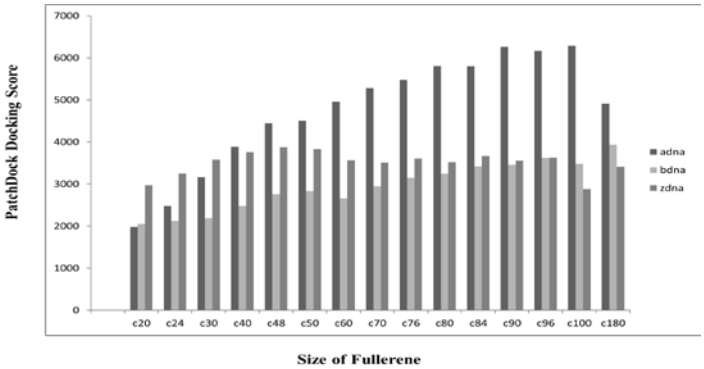

FIGURE 2: Effect of increase in molecular size of fullerene on the docking score with different forms of DNA

We have also studied that if there is any specificity in groove binding for fullerenes for all the three forms of DNA, as the width of groove depends upon the type of DNA. Fullerenes bind in both the

grooves i.e. mostly smaller fullerene bind in minor groove and bigger fullerene binds in major groove. In case of A-DNA all fullerenes (c20-c180) bind only in major groove. In B-DNA, C20 to C40 fullerene bind in minor groove whereas on further increase in the size of fullerene from C48 to 180, they bind in major groove.

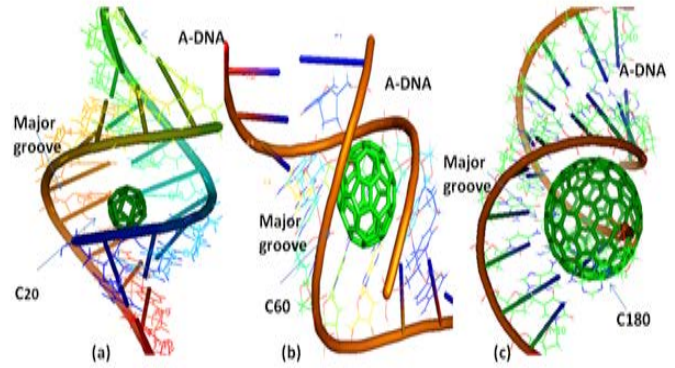

Figure 3: Interaction pattern of fullerenes of various sizes with A-form of DNA **(a)** C20 bound to major groove of A-DNA. **(b)** C60 bound to major groove of A-DNA **(c)** C180 bound to major groove of A-DNA.

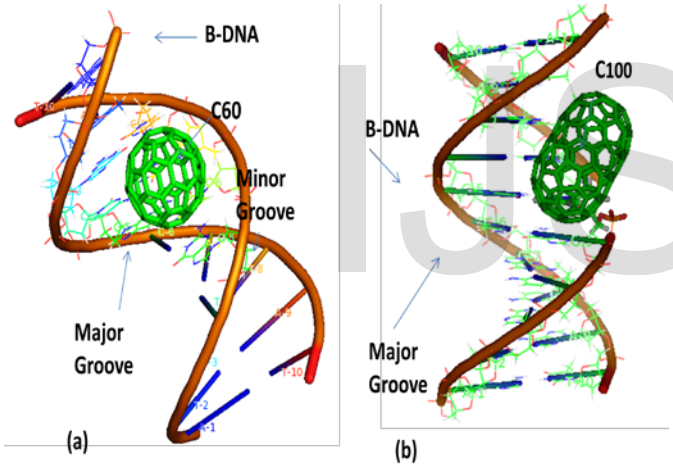

Figure 4: Interaction pattern of fullerenes of various sizes with B-form of DNA **(a)** C60 bound to major groove of B-DNA. **(b)** C100 bound to major groove of B-DNA.

In case of Z-DNA, pattern of effect of increasing molecular weight on groove binding was strange. C20 to C40 bind in major groove, but on further increase in the size of fullerene there is no regular pattern of binding i.e. C48 binds in minor groove but C50 binds in major groove. Again on increasing the molecular weight of fullerene binding occurs in minor groove from C60 to C180.

S.No.	Fullerenes	A-DNA Groove Binding	B-DNA Groove Binding	Z-DNA Groove Binding
1.	C20	Major	Minor	Major
2.	C24	Major	Minor	Major
3.	C30	Major	Minor	Major
4.	C40	Major	Minor	Major
5.	C48	Major	Major	Minor
6.	C50	Major	major/minor*	Major
7.	C60	Major	Major	Minor
8.	C70	Major	Major	Major
9.	C76	Major	major/minor*	Minor
10.	C80	Major	Major	Minor
11.	C84	Major	major/minor*	Minor
12.	C90	Major	Major	Minor
13.	C96	Major	Major	Minor
14.	C100	Major	Major	Minor
15.	C180	Major	Major	Minor

Note: '*' denotes binding occurs in both the grooves depending upon the nucleotide sequence.

TABLE 5: Effect of increase in molecular size of fullerene on Groove binding specificity.

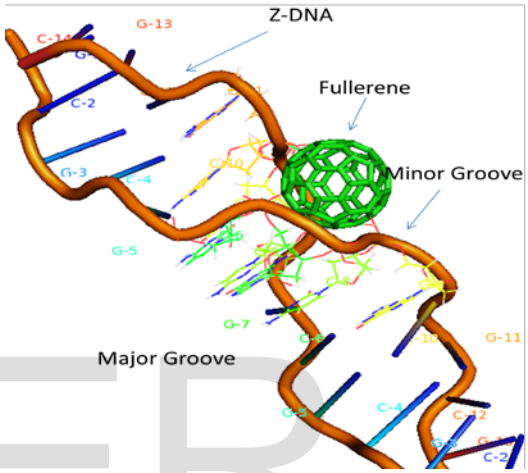

Figure 5- Interaction of C60 with Z-DNA. C60 is bound in major groove.

4 DISCUSSION

A number of previous studies have confirmed the interaction of C60, CNT's and carbon nanoparticles with DNA/RNA, leading to structural deformation of nucleotides [23, 24]. Some in vitro studies done to investigate the toxicity mechanism of C60 in biological system show that C60 molecules may interfere with the biological functions performed by DNA, resulting in disruptions to DNA replication, transcription, and repair processes [13]. More studies are needed to reveal the interactions of various species of fullerenes with DNA, and how this interaction may affect the biological functions. However to the best of our knowledge no such study has been done involving fullerene and fullerene family interaction with all the three types of DNA. Therefore, the present study was designed to reveal the effect of molecular weight and size of fullerene on its capacity to interact with different forms of DNA.

We have previously shown the applicability of PatchDock to determine interaction between nanoparticles and biomolecules [25]. In the present study, we performed molecular docking between various random sequences of all three forms (A, B & Z) of DNA with the fullerene molecules of different sizes ranging from C20 to C180. DNA do not posses complex structural feature including high density charge & chiral helix geometry. Although a number of chemicals are known to bind the double helix strand, but DNA don't posses any well defined binding site. Different organic molecules like aromatic and heterocyclic nucleic compounds are capable to form non-

covalent or covalent interactions in the minor and major grooves of DNA. Fullerene, a unique molecule of carbon shapes like hollow sphere, behaves like electron deficient electron donor, is overwhelmingly favorable for interaction with DNA. Previous studies have shown that the displacement of water molecules from the region between the nucleotides and the fullerenes were observed and this can be attributed to the large favorable interaction energies to hydrophobic interactions. The features of the DNA-C60 complexes depend on the nature of the nucleotides and this C60-ss-DNA binding can significantly deform the nucleotides and the capacity of C60 to deform the A form of DNA, whereas B & Z form are not affected by fullerene[13]. The results of our study also clearly show that the A-form of DNA was highly interactive with fullerene in contrast to B & Z form of DNA.

We analyzed the docking of various fullerene molecules with 10 different random sequence of DNA of all three forms, to analyze the effect of molecular weight of fullerene, its size, form of DNA, sequence of DNA etc. on the interaction capacity of fullerene with DNA. Our analysis of the docking study revealed that all the sizes of fullerene (C20-C180) bind both with A-form of DNA, whereas the B-form and Z-form of DNA interact with less binding energies with fullerene of all molecular weight. Further, with the increase of size of fullerene, the interaction energy of A-form of DNA also increases initially up to C90 and then start to decrease. Whereas with B-form of DNA the increase in size of fullerene causes somewhat continuous increase in docking score. In Z-form of DNA, the increase in size of fullerene did not show any regular increase or decrease in docking score.

Our results visibly disclose almost no effect of overall sequence variation of DNA on the binding energies of any size of fullerene. This could be because the fullerene molecules were found to involve mostly 1 to 2 base pairs (up to C80-C90). Although the results show that fullerene preferably bind to A-T pair, but only marginal difference in docking energies between A-T binding score and C-G binding score of one type of fullerene could be the reason for the overall effect of DNA sequence on docking score. With A-form of DNA, all sizes of fullerene docked in major groove. Probably the narrow and deep shape of major groove fits and holds the fullerene geometrically, whereas the minor groove being broad and shallow fails to give a better grip to fullerene molecules. As the minor groove are narrow with size range of 6-9 Å the smaller fullerene (up to size C90 approx 8-9 Å) [26] are fitting better therefore docking well, but further increase in size is probably not allowing the proper docking as narrow shape of groove, reducing the docking score. Whereas, with B-form DNA the major groove are wide and deep, therefore all the fullerene sizes under study are fitting well in the groove, resulting in regular increase in docking score with increase in fullerene size. Although the overall docking score with B-form of DNA is less than with that of A-form, the reason could be the wide size of groove in B-DNA.

CONCLUSION

Binding score increases with the increase in the molecular weight of the fullerene while interacting with A & B-form of DNA but Z-form of DNA shows no regular pattern of binding. Number of interacting base pairs increases as the molecular size of fullerene increases. But no such change in the binding score was observed with the change in the sequence of DNA. In fact, the groove binding depends on the form of DNA, fullerene and fullerene family binds in major groove of A-DNA while binds in both major and minor grooves in B and Z-form of DNA.

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